PATENT COOPERATION TREATY

From the
INTERNATIONAL PRELIMINARY EXAMINING AUTHORITY

PCT

To:

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WRITTEN OPINION
(PCT Rule 66)

Date of mailing *(day/month/year)*	25.08.2004
Applicant's or agent's file reference HSM-LUP-GYR	**REPLY DUE** **within 2 month(s) and 15 days** from the above date of mailing

International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/IN 02/00192	20.09.2002	20.09.2002

International Patent Classification (IPC) or both national classification and IPC
C07K16/12

Applicant
LUPIN LTD

1. This written opinion is the **second** drawn up by this International Preliminary Examining Authority.

2. This opinion contains indications relating to the following items:

I	☒	Basis of the opinion
II	☐	Priority
III	☒	Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
IV	☐	Lack of unity of invention
V	☒	Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
VI	☐	Certain documents cited
VII	☐	Certain defects in the international application
VIII	☐	Certain observations on the international application

3. The applicant is hereby **invited to reply** to this opinion.

When? See the time limit indicated above. The applicant may, before the expiration of that time limit, request this Authority to grant an extension, see Rule 66.2(d).

How? By submitting a written reply, accompanied, where appropriate, by amendments, according to Rule 66.3. For the form and the language of the amendments, see Rules 66.8 and 66.9.

Also: For an additional opportunity to submit amendments, see Rule 66.4. For the examiner's obligation to consider amendments and/or arguments, see Rule 66.4 bis. For an informal communication with the examiner, see Rule 66.6.

If no reply is filed, the international preliminary examination report will be established on the basis of this opinion.

4. The final date by which the international preliminary examination report must be established according to Rule 69.2 is: 20.01.2005

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I. Basis of the opinion

1. With regard to the **elements** of the international application *(Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this opinion as "originally filed")*:

Description, Pages

1-3, 5-12, 14-18	as originally filed
4, 13	received on 28.07.2004 with letter of 26.07.2004

Sequence listings part of the description, Pages

1-3	as originally filed

Claims, Numbers

1-5, 7	as originally filed
6, 8	received on 28.07.2004 with letter of 26.07.2004

Drawings, Sheets

1/7-7/7	as originally filed

2. With regard to the **language**, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.

   These elements were available or furnished to this Authority in the following language: , which is:

   - ☐ the language of a translation furnished for the purposes of the international search (under Rule 23.1(b)).
   - ☐ the language of publication of the international application (under Rule 48.3(b)).
   - ☐ the language of a translation furnished for the purposes of international preliminary examination (under Rule 55.2 and/or 55.3).

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

   - ☒ contained in the international application in written form.
   - ☐ filed together with the international application in computer readable form.
   - ☐ furnished subsequently to this Authority in written form.
   - ☒ furnished subsequently to this Authority in computer readable form.
   - ☐ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.
   - ☒ The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. The amendments have resulted in the cancellation of:

   - ☐ the description, pages:
   - ☐ the claims, Nos.:

☐ the drawings, sheets:

5. ☐ This opinion has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)).

6. Additional observations, if necessary:

see separate sheet

III. Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

1. The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non-obvious), or to be industrially applicable have not been and will not be examined in respect of:

☐ the entire international application,

☒ claims Nos. 1-4, 7 (in part)

because:

☐ the said international application, or the said claims Nos. relate to the following subject matter which does not require an international preliminary examination (specify):

☐ the description, claims or drawings *(indicate particular elements below)* or said claims Nos. are so unclear that no meaningful opinion could be formed *(specify)*:

☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.

☒ no international search report has been established for the said claims Nos. 1-4, 7 (in part)

2. A written opinion cannot be drawn due to the failure of the nucleotide and/or amino acid sequence listing to comply with the Standard provided for in Annex C of the Administrative Instructions:

☐ the written form has not been furnished or does not comply with the Standard.

☐ the computer readable form has not been furnished or does not comply with the Standard.

V. Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Claims	
Inventive step (IS)	Claims	6
Industrial applicability (IA)	Claims	

2. Citations and explanations

see separate sheet

Re Item I

Basis of the report

The amendment of page 13 of the description, line 18, as submitted with the letter dated 26 July 2004 as "corrected page 13" does not comply with the amendment discussed in said letter. On the "corrected page 13", the subject-matter is a "neutralizing **monoclonal** antibody, scFv:GyrA", while in the letter a "neutralizing single chain antibody, scFv**A**:GyrA" is discussed. With regard to what has originally been disclosed in the description, the subject-matter appears to be a "neutralizing single chain antibody, scFv:GyrA". The statement as to admissibility of the amendments given under item III.1 will refer to a "neutralizing single chain antibody, scFv:GyrA".

Re Item III

Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

As outlined in the International Search Report (ISR) the search for claims 1-4 has been restricted to those parts of the claims which appear to be clear, supported and disclosed in the sense of Articles 5 and 6 PCT, namely to the single chain antibody containing amino acid sequences SEQ ID NOS: 3 and 4 or having amino acid sequence SEQ ID NO: 2.

The same applies to the search for claim 7 which has been restricted to the monoclonal antibodies MsGyrA:C3 and MsGyrA:H11.

The International Preliminary Examining Authority fully supports the objections made in the ISR. The Applicant's attention is drawn to the fact that claims, or parts of claims, relating to inventions in respect of which no ISR has been established need not to be the subject of an International Preliminary Examination (Rule 66.1(e) PCT). The Applicant is advised that the EPO policy when acting as an International Preliminary Examining Authority is normally not to carry out a preliminary examination on matter which has not been searched. This is the case irrespective of whether or not the claims are amended following receipt of the ISR or during Chapter II procedure.

Re Item V

Reasoned statement with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

The opinion expressed as to novelty, inventive step and industrial applicability refers only to matter for which an ISR has been drawn up.

Reference is made to the following document:

D1: MANJUNATHA, U. H. ET AL.: "Monoclonal antibodies to mycobacterial DNA gyrase A inhibit DNA supercoiling activity", EUROPEAN JOURNAL OF BIOCHEMISTRY, vol. 268, no. 7, April 2001 (2001-04), pages 2038-2046

1. Amendments (Article 34(2)(b) PCT)

The amendments filed with the letter dated 26 July 2004 are allowable, since they do not introduce subject-matter which extends beyond the content of the application as filed (Article 34(2)(b) PCT).

On page 4, line 18, the invention has been restricted to the "inhibition of DNA supercoiling activity catalyzed by *M. tuberculosis* DNA gyrases by full-length mAb and its Fab" instead of "inhibition of DNA supercoiling activity catalyzed by *M. smegmatis* and *M. tuberculosis* DNA gyrases by full-length mAb and its Fab".

The amendments of page 18, lines 15-20, include the replacement of the wording "coding" by "encoding" (line 15) and, as discussed under item I, the replacement of the wording "monoclonal antibody, MsGyrA:C3" by "single chain antibody, scFv:GyrA" (line 18).

Claim 6 has been corrected to pertain to "fusing said variable heavy chain and light chain regions" instead of "fusing said variable heavy chain region and light regions".

In claim 8, a functional feature ("which inhibits the activity of DNA gyrase from *M. smegmatis* and *M. tuberculosis*") of the claimed plasmid has been deleted, while it is still characterized by the technical feature "encodes an engineered single chain antibody containing amino acid sequence for inhibiting the activity of DNA gyrase from *M. smegmatis* and *M. tuberculosis*, said amino acid sequences being as shown in SEQ

ID NOS: 3 and 4 respectively".

2. Inventive Step (Article 33(3) PCT)

The argumentation given by the Applicant's Representative in the letter dated 26 July 2004 has been taken into account. However, it is to be noted that in **D1** the monoclonal antibodies MsGyrA:C3 and MsGyrA:H11 are explicitly mentioned to "form a new class of **inhibitors specific for mycobacterial DNA gyrase**" (page 2045, column 1, lines 12-14). Further, the authors state that "As the GyrA-specific mAbs described here **interact with GyrA from *M. tuberculosis*, *M. bovis*, *M. leprae* and *M. avium***, it opens the avenue to explore their potential value in the diagnosis of mycobacterial infections. It is clear that these mAbs would serve as invaluable tools to **study the enzyme in detail to address the role of DNA gyrase in the biology of mycobacteria**." (page 2045, column 1, lines 33-40). Moreover, the mAbs are described to be "useful for characterizing different complexes and interactions in which DNA gyrase is involved ... (and) there is a potential to use the information to develop peptide inhibitors for DNA gyrase as a first step towards lead molecule discovery. The latter point attains considerable significance due to the alarming increase in drug-resistant **tuberculosis** in recent years" (page 2045, column 1, lines 42-48).

In the light of D1, the skilled person would expect that the inhibition of *Mycobacterium smegmatis* enzyme utilizing the said mAbs could be extrapolated to similar inhibition of *Mycobacterium tuberculosis* DNA gyrase. Following standard methods well established in the prior art, a skilled person would make use of such mAbs in order to prepare any engineered single chain antibodies inhibiting the activity of DNA gyrase from *Mycobacterium smegmatis* and *Mycobacterium tuberculosis*.

However, in agreement with the line of reasoning given by the Applicant's Representative, the preparation of the **engineered single chain antibody of present application, namely the single chain antibody containing amino acid sequences SEQ ID NOS: 3 and 4 or having amino acid sequence SEQ ID NO: 2**, is considered to be novel and inventive. In other words, **the restriction of the claimed scope to what has been actually disclosed in the description would render the objection obsolete**.